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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/808,827	02/28/97	GUNZBURG W	GSF97-01A

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EXAMINER	
BRUSCA, J	
ART UNIT	**PAPER NUMBER**
1631	24

DATE MAILED: 04/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/808,827	Gunzburg et al.
Examiner	**Group Art Unit**
John S. Brusca	1631

☒ Responsive to communication(s) filed on *3/7/00*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 5, 7, 9-26, 28, 29, 31, and 32* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 5, 7, 9-26, 28, 29, 31, and 32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The group and or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1631.

Priority

2. The instant application properly claims priority to International Application PCT/EP95/03445 under 35 U.S.C. § 120 and to Danish Application No. 1017/94.

Oath/Declaration

3. The supplemental Rule 63 Declaration received 3/28/00 has been entered to the instant application. The supplemental declaration properly claims priority to International Application PCT/EP95/03445, of which the instant application is a continuation-in-part.

Claim Objections

4. The objections to claims 5 and 16 in the Office Action mailed 8/31/99 is withdrawn in view of the Amendment received 3/7/00.

Claim Rejections - 35 USC § 112

5. The rejections of claims 1, 5, 8-19, 22-26, 29, 31, and 32 under 35 U.S.C. § 112, second paragraph in the Office Action mailed 8/31/99 is withdrawn in view of the Amendment received 3/7/00 and the prior cancellation of claim 8 in the Amendment received 5/10/99.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 7, 20, and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites the limitation "said regulatory element."There is insufficient antecedent basis for this limitation in the claims. Claim 1 provides antecedent basis for a heterologous promoter. Claim 31 (dependent on claim 1) provides antecedent basis for said promoter. Claim 7 (dependent on claim 31) refers to said regulatory element which lacks antecedent basis. Claim 7 further discusses regulatory elements selected from groups comprising regulatory elements and promoters, and is therefore indefinite because regulatory elements appear to be distinguished from promoters in the claim, and therefore regulatory elements cannot be selected from a member of a group comprising a promoter. The suggestion of a remedy in the Office Action mailed 8/31/99 was in error regarding this point.

Claims 20 and 21 are indefinite because it is not clear whether the claims read on introduction of a retroviral vector into an animal. The rejection would be overcome by amending

claim 20 to clearly read on cells in an animal or cultured cells. The suggested remedy in the Office Action mailed 8/31/99 was not adopted as written.

For the purpose of examination, the claims have been assumed to incorporate the suggested amendments.

Claim Rejections - 35 USC § 102

8. The rejection of claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 under 35 U.S.C. 102(b) as being anticipated by Couture et al. is withdrawn in view of the Amendment received 3/7/00.

9. The rejection of claims 13 and 14 under 35 U.S.C. 102(b) as being anticipated by Couture et al. in light of Miller et al. and Panganiban et al. '84 cited in the Form PTO 892 in the Office Action mailed 3/16/98) is withdrawn in view of the Amendment received 3/7/00.

Claim Rejections - 35 USC § 103

10. The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Price et al. (cited in the Form PTO 892 in the Office Action mailed 3/16/98) is withdrawn in view of the Amendment received 3/7/00.

11. The rejection of claims 15, 20, 21, and 26 under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Longmore et al. and Kay et al. (both cited in the Form PTO 892 in the Office Action mailed 3/16/98 in view of the Amendment received 3/7/00.

12. The rejection of claim 7 under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Mee et al. (cited in the Form 892 in the Office Action mailed 3/16/98 is withdrawn in view of the Amendment received 3/7/00.

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al.

Couture et al. (Reference AS in the Form PTO-1449 filed 9/23/97) shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses, including leukemia and sarcoma retroviruses. Couture et al. shows on page 669 column 2 that the first 40 nucleotides of the original vector are retained in the

substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene and a neomycin resistance gene, which are considered to be cellular sequences. Couture et al. shows in the abstract that after packaging, the substituted U3 region appears at the 5' LTR and serves as a promoter for all genes in the body of the vector, and that different LTR constructs were preferentially expressed in specific cell types. Couture et al. states in the second paragraph of the Results section on page 669 that U3 regions are bound by cellular factors. Couture et al. shows in Table 3 that their chimeric LTR promoters are active in a cell type specific manner. Couture et al. state on page 670 that promoter suppression or interference may occur within retroviral vectors containing internal promoter elements. Couture et al. states on page 667 that retroviral vectors with target cell specificity have utility in gene therapy protocols. Couture et al. shows the use of packaging cell lines PA317 and GP&E86 on page 669 to package their retroviral vectors. Couture et al. does not show a vector comprising a multiple cloning site in the U3 region.

Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella

et al. because Faustinella et al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

15. Claims 13 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further as evidenced by Miller et al. and Panganiban et al.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above do not explicitly show an altered retroviral gene or a partially deleted sequence involved in integration of retroviruses.

Couture et al. shows in figure 1 a retroviral vector LCSN and a derivative of LCSN. Couture et al. shows in the Methods section on page 668 that their vectors are derivatives of the vectors of Miller et al.

Miller et al. shows in figure 2 that their vectors retain the phi+ packaging sequence, but lack the gag, pol, and env genes of a replication-competent retrovirus.

Panganiban '84 shows that the 3' end of the pol gene encodes the int locus that is required for integration of the reverse transcribed retroviral genome to form a provirus.

Therefore the vectors of claims 13 and 14 are taught by Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further as evidenced by Miller et al. and Panganiban et al.

16. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Price et al.

Claim 10 is drawn to the vector of claim 1 further limited to a vector derived from a BAG vector.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show a vector derived from a BAG vector.

Price et al. shows a BAG retroviral vector comprising a beta galactosidase reporter gene, and that the vector can be used to identify cells and progeny of cells infected with the vector.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above by basing the construction on a BAG vector of Price et al. because Price et al shows that a vector with a beta-galactosidase reporter gene may be used to identify cells and progeny of cells infected with the vector.

17. Claims 15, 20, 21, and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Longmore et al. and Kay et al.

Claim 15 is drawn to the vector of claim 1 comprising a DNA fragment homologous to a cellular sequence. Claim 20 is drawn to a method of introducing nucleotide sequences by infection with the retroviral vector of claim 17 in humans or animals or cultured cells of humans or animals.

Claim 21 is drawn to the method of claim 20 further limited to comprise genes, regulatory sequences, or promoters. Claim 26 is drawn to a pharmaceutical comprising the retrovirus of claim 22.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show use of retroviral vectors in an animal.

Longmore et al show in the abstract that mice infected with a retroviral vector expressing the erythropoietin receptor had increased platelet counts and splenic megakaryocytes.

Kay et al. shows in the abstract and throughout that hemophiliac dogs infected with a retroviral vector expressing factor IX shows improved levels of clotting and thromboplastin times for greater than 5 months after treatment.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above to express a therapeutic protein because both Kay et al. and Longmore et al. show that retroviral vectors may be used to express therapeutically effective levels of a recombinant protein in an animal. Regarding the limitation in claim 15 to a vector comprising a DNA fragment homologous to a cellular sequence, the erythropoietin receptor gene of Longmore et al. or the factor IX gene of Kay et al. teach such a sequence in a retroviral vector.

18. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above, and further in view of Mee et al.

Claim 7 is drawn to the vector of claim 5 further limited to a target sell specific regulatory element and promoter selected from the group consisting of Whey Acidic Protein specific regulatory elements and promoters, Mouse Mammary Tumor Virus specific regulatory elements and promoters, beta lactoglobulin and casein specific regulatory elements and promoters, pancreas specific regulatory elements and promoters, lymphocyte specific regulatory elements and promoters, and mouse mammary tumor virus specific regulatory elements and promoters conferring responsiveness to glucocorticoid hormones or directing expression to the mammary gland.

Couture et al. in view of Faustinella et al. as applied to claims 1, 5, 8, 9, 11, 12, 15-19, 20-25, 28, 29, 31, and 32 above does not show the claimed promoter or regulatory elements.

Mee et al. shows a retroviral vector comprising a mouse mammary tumor virus LTR, and that the LTR expressed a gene after induction with dexamethasone. Mee et al. state on page 292 that their vector is a potentially powerful tool for the manipulation of gene expression in a variety of cell types.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vector of Couture et al. by insertion of a promoter region in a deleted 3' U3 region of a retroviral vector results in the expression of vector genes under the control of the

inserted promoter in a cell type specific manner because Mee et al. show that their LTR promoter may be used to manipulate gene expression in a variety of cell types.

19. Applicant's arguments filed 3/7/00 have been fully considered but they are not persuasive.

The Applicants state that Couture et al. does not show a partial deletion of a U3 region, however such a deletion is taught on page 669, column 2 as noted above.

Conclusion

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Certain papers related to this application may be submitted to Art Unit 1631 by facsimile transmission. The FAX number is (703) 305-7939. In such cases please call the Examiner at (703)

308-4231 at the time of transmission to expedite delivery of the fax. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6 (d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John S. Brusca

John S. Brusca, Ph.D.

Primary Examiner